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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 121003

Application Number: 09/526,320
Filing Date: March 15, 2000
Appellant(s): GABRILOVICH ET AL.

Charles P. Landrum

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 8/22/03.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is incorrect. The first two sentences of this section of the brief are correct in that claims 1-11, 15-22, 24, 26-31, 33-37, and 61-135 were pending at the time of filing of the final Office action mailed on 12/12/02, and that the applicant's after-final amendment filed concurrently with the appeal brief requests the cancellation of non-elected claims 5-10 and 61-135. Please note that Appellant's after-final amendment has been entered and claims 5-10 and 61-135 have in fact been canceled. The third sentence in the appellant's Status of the Claims section is incorrect as it states that claims 1-4, 11, 15-22, 24, 26-31 and 33-37 were pending at the time of the final Office action. As noted above, claims 1-11, 15-22, 24, 26-31, 33-37, and 61-135 were pending at the time of filing of the

final Office action mailed on 12/12/02. Now, at the time of appeal and following the entry of appellant's after final amendment, claims 1-4, 11, 15-22, 24, 26-31 and 33-37 are pending.

A correct statement of the status of the claims is as follows:

This appeal involves claims 1-4, 11, 15-22, 24, 26-31, and 33-37.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct. As noted above, appellant's after final amendment submitted with the Appeal Brief on 5/14/03 has been entered and claims 5-10 and 61-135 have been cancelled.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 1-4, 11, 15-22, 24, 26-31 and 33-37 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Art of Record

Hurpin et al. "The mode of presentation and route of administration are critical for the induction of immune responses to p53 and antitumor immunity " Vaccine, Vol. 16 (1998) pp. 208-215.

Restifo et. al. "Molecular Mechanisms Used by Tumors to Escape Immune Recognition: Immuno gene therapy and the cell biology of Major Histocompatibility complex Class 1 " Journal of Immunotherapy, Vol. 14 (1993), pp. 182-190.

Deonarain et al. "Ligand-targeted receptor-mediated vectors for gene delivery" Exp. Opin. Ther. Patents, Vol. 8, No. 1 (1998), pp. 53-69.

Miller et.al. "Targeted vectors for gene therapy" FASEB J, Vol. 92 (1995), pp. 190-199.

Orkin et al. "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy" (December 7, 1995), pp. 1-39.

Marshall et al. "Gene Therapy's Growing Pains" Science, Vol. 269 (August 1995), pp. 1050-1055.

Verma et al. "Gene Therapy-Promises, Problems and Prospects" Nature, Vol. 389 (September 1997), pp. 239-242.

Vogelstein et al. "The multistep nature of cancer" Trends in Genetics, Vol. 9, No. 4 (1993), pp. 138-141.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-4, 11, 15-22, 24, 26-31 and 33-37 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is set forth below and in prior Office actions mailed on 9/28/01, 6/26/02 , and 12/12/02.

The claims as amended recite methods of treating a human subject having or suspected of having cancer or pre-cancerous disease comprising the steps of (i) identifying a subject having cancer or pre-cancer characterized by an alteration or increased expression of a self gene product and (ii) intradermally administering to said subject an expression construct in an adenovirus particle comprising a self gene under the control of a promoter wherein dendritic cells are infected by said construct, and whereby said self gene product is expressed by dendritic cells and is capable of stimulating an anti-self gene product immune response. Dependent claims further recite wherein the self-gene product is an oncogene, such as a tumor suppressor, tumor associated gene, growth factor, nuclear factor (claims 2-4), and wherein the gene product is p53 (claim 5).

Please note that an election of species requirement over the genus of "self gene product" was made over the instant appealed claims in the Restriction Requirement mailed to the appellants on 6/20/01. In response to this requirement received on 8/22/01, the appellants elected the species of "tumor suppressor genes" for examination on the merits. While claims 4 and 5 are limited to the elected species, claims 1-3, 11, 15-22, 24, 26-31 and 33-37 are not limited to the elected subject matter and continue to recite the generic "self gene product". It is the finding of the Office that the specification neither enables the use of the elected species of "tumor suppressor genes" or the genus of "self gene products" in the methods as claimed.

The claims as amended are limited to the administration of an expression construct in an adenovirus particle. The original claims read broadly on the administration of any expression construct. As a result, previous office actions indicated that while the specification and prior art of record provide enablement for methods of generating anti-tumor immune responses by

intradermal administration of a plasmid vector encoding p53, the specification does not provide an enabling disclosure for practice of the claimed methods using viral vectors or particles. As indicated above, the claims on appeal specifically recite the intradermal administration of a recombinant adenoviral particle. The rejection as it stands is based on the amended claims on appeal. Thus, the issue at hand is whether the specification provides an enabling disclosure for treating cancer or pre-cancer by intradermally administering a recombinant adenovirus which encodes a self gene product associated with cancer or pre-cancer in a human subject.

The Office has analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement for the scope of the instant methods. The Wands analysis and supporting specific evidence are presented below for the single remaining issue.

Guidance provided by the specification and working examples

The specification generally teaches that expression constructs encoding self-gene products associated with cancer can be administered to a subject resulting in the generation of specific CTL responses capable of having a therapeutic effect on a tumor overexpressing or having a mutation in the self-gene product. In particular, the specification teaches the introduction of the expression construct encoding the self gene product to dendritic cells either *in vitro* or *in vivo*. The specification also discloses that a preferred embodiment of the invention includes the intradermal administration of the expression constructs. The specification provides several working examples of the instant invention which are limited to *ex vivo* methods of

administering splenic or bone-marrow derived dendritic cells transduced *in vitro* with an adenoviral vector encoding p53 under control of the CMV I/E promoter to mice. The working examples demonstrate that the intravenous, subcutaneous, or intraperitoneal injection of *in vitro* transduced dendritic cells (DCs) with adenovirus p53 results in the generation of p53 specific CTL, and in the case of mice which received intravenous administration of the transduced DCs, inhibition of growth of a p53 positive tumor. It is noted that the specification does not provide any working examples which utilize intradermal injection, or which involve the direct injection of any type of expression construct encoding p53 or any other tumor suppressor gene, or self-gene product. Thus, the guidance provided by the specification for the direct intradermal administration of an adenovirus encoding a self gene product is entirely prophetic and not exemplified in the working examples. Further, the direct administration of adenovirus and the administration of dendritic cells infected with an adenovirus *in vitro* are not equivalent and a nexus cannot be drawn between applicant's *ex vivo* results and the instant methods of treating cancer by direct intradermal injection of an adenovirus comprising expression constructs. Infection of dendritic cells *in vitro/ex vivo* occurs under artificial cell-culture conditions which allow for direct contact of the dendritic cells with optimized levels of the virus. The cells are then further manipulated *in vitro* to generate a population of cells which are known to express the encoded gene vector prior to their introduction into the subject. In contrast, the transduction of dendritic cells *in vivo* by direct administration of the adenovirus to the subject is affected by the rate of clearance of the vector from the injection site, the tropism of the vector for the target cell, the rate of cell transduction under physiological conditions, and the presence of any pre-existing immune responses to the virus itself. The specification does not provide sufficient guidance for

the targeted transduction of dendritic cells following intradermal administration of an adenovirus. The specification only states generally that dendritic cells will be infected following intradermal injection or infusion of a recombinant adenovirus. Based on these substantial differences, a nexus between the *ex vivo* working examples and the *in vivo* methods as claimed cannot be found. Thus, appellant's working examples do not provide enabling support for the methods of treating cancer as claimed.

Nature of the invention

The premise of the instant invention as claimed is that the intradermal administration of an adenovirus encoding a self gene product results in the infection of dendritic cells which then stimulate immune response against the self gene product which are capable of treating a tumor which overexpresses or has a mutation in a self gene product. At the time of filing, the art teaches that the regulation of cell growth is a complex process involving numerous inter- and intracellular interactions. Disregulation of this process through genetic mutation results in neoplasia. As Vogelstein et al. explains, " each individual cancer arises not from a single mutation, but from the accumulation of several mutations" (Vogelstein et al. (1993) Trends in Genetics, Vol. 9(4), page 138, lines 9-11). A corollary to this principle is that each type of tumor, lung versus colon, versus lymphoid, may have different sets of mutations. In general, two major categories of mutations can be found in transformed cells, mutations in tumor suppressor genes, and mutations in oncogenes. Vogelstein et al. teach that while the mutation of the abl oncogene to c-abl can be found in many chronic myelogenous leukemias, mutations in the tumor suppressor gene APC are more common in colorectal tumors (Vogelstein et al. (1993) Trends in Genetics, Vol. 9(4), page 140, column 2, paragraphs 2-3, and page 141, column 1, paragraphs 1-

2). In addition, individual transformed cells of a tumor acquire new mutations over time, resulting in clonal subsets with differential sensitivities to drugs, radiation, and immune attack (Vogelstein et al. (1993) Trends in Genetics, Vol. 9(4), page 141, column 1, paragraph 1). Thus, successful use of the instant invention for the treatment of a particular tumor by administration of a wild type tumor suppressor gene would require detailed knowledge of the genetic mutations of a particular type of tumor in order to insure that any immune responses generated against the vector expressed tumor suppressor gene would recognize the target tumor cell. In addition, cancer immunotherapy using tumor associated antigens is further complicated by the fact that in order for the tumor antigen specific T cells to be effective against the tumor, the tumor must be able to express recognizable levels of peptide/MHC class I complexes derived from tumor antigen. At the time of filing, the art teaches that tumors evade immune responses by a variety of mechanisms including down-regulation of TAP and MHC-encoded proteasome components, loss of antigenic epitopes by either lack of expression or mutations, loss of functional β_2m expression , and loss of particular MHC class I alleles (Restifo et al (1993) J. Immunother., Vol. 14, page 183, col 1, lines 8-14, and page 184, col. 2). The loss or mutation of any of these molecules would prevent the tumor cells from being recognized by the tumor specific cytotoxic T cells. Furthermore, immunotherapy based on self gene products is complicated by the limited immunogenicity of self antigens. At the time of filing, immune tolerance towards self gene products was a well accepted concept. Generation of immune responses against self antigens requires breaking immune tolerance. The applicant's working examples, as discussed above, are limited to the generation of anti-p53 immune responses to tumor which overexpress p53 and are capable of presenting p53 peptides for recognition by anti-p53 CTL by using dendritic cells

which have been transduced *ex vivo* to express p53. In view of the nature of generating immune responses against tumor associated self antigens, and the nature of mechanisms by which tumor cells evade immune responses, the specification and working examples do not provide sufficient guidance to establish the predictability of treating a cancer or pre-cancerous disease in a human by intradermal administration of an adenovirus encoding a self gene product.

State of the Prior Art

The state of the art of gene therapy and immunotherapy of cancer at the time of filing is also relevant to the analysis of the specification for enablement of the instant claims. The effective filing date of the instant application is March 15, 1999. At the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any

gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2).

Furthermore, as noted above, the claims as written recite the limitation that dendritic cells are infected with the recombinant adenovirus following intradermal administration. At the time of filing , the skilled artisan did not consider the targeting of vectors to specific cell types *in vivo* to be predictable . Deonarain, in a review entitled, " Ligand-targeted receptor-mediated vectors for gene delivery", teaches that one of the main obstacles to successful gene therapy is, " ... the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time", and states that, " .. even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" (Deonarain et al. (1998) Exp. Opin. Ther. Patents, Vol. 8 (1), page 53, lines 1-4, and page 54, lines 12-15). Miller et al. concurs, teaching that the development of surface targeting has been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since , " attainment of one usually compromises the other" (Miller et al. (1995) FASEB, Vol. 9, page 198, paragraph 2). As discussed above, the specification does not provide guidance in the form of detailed teachings or specific working examples for methods to target any vector including an adenoviral vector to dendritic cells *in vivo*, or demonstrate that adenoviruses have natural tropism for dendritic cells *in* vivo, particularly following intradermal administration.

The prior art of record further provides specific and substantial evidence that intradermal injection of a virus encoding the p53 tumor suppressor does not in fact result in anti-p53 immune responses or treatment of p53 expressing tumors. Hurpin et al. provides specific evidence that the

intradermal injection of a viral vector, vaccinia virus, encoding p53 is completely ineffective in generating either anti-53 antibodies or CTL (Hurpin et al. (1998) Vaccine, Vol. 16, No. 2/3, 208-215, see page 210, column 2, and page 211, Figure 1). Note in particular that the level of CTL response following intradermal injection of the recombinant vaccinia virus encoding p53 is actually lower than the background response obtained from immunization with empty vector. Based on these results, the skilled artisan would not have predicted at the time of filing that recombinant viruses encoding a tumor suppressor gene could generate therapeutic anti-tumor immune responses following intradermal injection. In fact, the appellants themselves concur with this conclusion. In analyzing the teachings of Hurpin et al., the appellants concluded that, " Hurpin teaches that intradermal injection of canarypox virus does **not** work, whereas intradermal injection of naked DNA does. Thus, one skilled in the art would not expect success generally, much less success using another virus like adenovirus" (Appellant's arguments received on 4/8/02, page 16). Therefore, the combined evidence of the prior art teachings as discussed above establishes the absent evidence to the contrary the skilled artisan would have considered methods of treating cancer by intradermal administration of an adenovirus encoding a self gene product, and more specifically a tumor suppressor gene product, as unpredictable.

Conclusion

Having properly analyzed the specification for providing an enabling disclosure for the breadth of the claims as written, the office finds the following: based on the art recognized unpredictability in achieving targeted gene delivery *in vivo* using vectors currently available at the time of filing, the art recognized unpredictability of immunotherapy of cancer, the nature of self antigens and tumors, the breadth of the claims, the absence of guidance for the targeted

transduction of dendritic cells *in vivo* using an adenovirus wherein the resulting transduced dendritic cells are capable of generating a therapeutic anti-tumor immune response, and the evidence of record that intradermal injection of recombinant viruses encoding p53 does **not** result in anti-p53 immune responses, it would have required undue experimentation for the skilled artisan at the time of filing to practice the instant methods as claimed.

(11) Response to Argument

Appellant's arguments have been fully considered but have not been found persuasive in overcoming the grounds of rejection of the claims presented above for reasons discussed in detail below.

The appellant argues that the Office has failed to provide "substantial evidence" in support of the finding of lack of enablement of the claims, citing *In re Gartside*, 203 F.3d 1305, 1315 (Fed. Cir. 2000). The appellant further argues that the findings of fact and conclusion of law by the PTO must be made in accordance with the Administrative Procedure Act, 5 U.S.C. 706(A), (E), 1995, citing *Dickinson v. Zurko*, 527 U.S. 150, 158 (1999). In regards to the comments made by the applicants that the office has not met its burden in questioning the enablement provided in the specification for the instant invention, it is noted that the office action has analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working

examples, and presented detailed scientific reasons supported by publications from the art for the finding of a lack of enablement for the scope of the instant methods. It is also noted that case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). 35 U.S.C. 112 also requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Ultimately, ".. the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970. Based on the Wands analysis of the instant specification, see section (10) above, the scope of the instant claims does not bear a reasonable correlation to the scope of enablement provided by the specification and as such does not meet the requirements of 35 U.S.C. 112, first paragraph.

The appellant further argues that no evidence has been provided which demonstrates that the skilled artisan could not use the invention as claimed to treat cancer and that examples need not be presented for every embodiment of the invention, *In re Borkowski* . While the Office agrees that working examples are not required, ".. the lack of working examples, is, nevertheless, a factor to be considered in a case involving both physiological activity and an undeveloped art. When a patent applicant chooses to forego exemplification and bases utility on broad terminology and general allegations, he runs the risk that unless one with ordinary skill in the art

would accept the allegations as obviously valid and correct, the examiner may, properly, ask for evidence to substantiate them". *Ex parte Sudilovsky* (BdPatApp&Int) 21 USPQ2d 1702, citing *In re Novak*, 306 F.2d 924, 134 USPA 335 (CCPA 1962) 4 and *In re Fouche*, 439 F.2d 1237, 169 USPQ 429 (CCPA 1971). Furthermore, in response to the appellant's contention that the Office has not provided sufficient evidence, it is noted that in fact the Office has provided a detailed analysis of the claimed invention and provided specific evidence in the form of scientific arguments and printed publications that properly challenge the enablement of the specification for methods of treating cancer or a pre-cancerous disease by intradermal administration of an adenovirus encoding a self gene product, and in particular a tumor suppressor gene product (see the office actions mailed on 6/26/02 and 12/12/02 and section (10) above).

The appellant also argues that the references previously cited in support of the unpredictability of gene therapy of cancer, Verma et al., Orkin et al., and Marshall et al., speak to problems with "optimization" of gene therapy and not "operability", which applicants state is the correct standard for enablement, citing *In re Marzocchi*. Please note that applicant's methods recite the treatment of cancer. Thus, the "operability" of the instant methods rests on whether following the method steps as claimed will actually result in the treatment of cancer in the human host. Verma et al., Orkin et al., and Marshall et al., were cited to establish the state of the art of *in vivo* therapeutic gene delivery at the time of filing. As stated in previous office actions, the combined teachings of Verma et al. Orkin et al., and Marshall et al. demonstrate that at the time of filing, gene therapy of disease was not considered an established and predictable therapeutic strategy for diseases including cancer. The fact that Marshall et al. concludes that "many problems must be solved before gene therapy will be useful for more than the rare application"

(Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1), and Orkin et al. states that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" clearly demonstrates that gene therapy was not considered predictably operable at the time of filing. Furthermore, the Office has cited Hurpin et al. as specific evidence that the intradermal injection of a viral vector, vaccinia virus, encoding p53 is completely ineffective in generating either anti-53 antibodies or CTL (Hurpin et al. (1998) Vaccine, Vol. 16, No. 2/3, 208-215, see page 210, column 2, and page 211, Figure 1). In particular, it was noted that the level of CTL response following intradermal injection of the recombinant vaccinia virus encoding p53 is actually lower than the background response obtained from immunization with empty vector. As discussed in detail in section (10) above, the appellant's themselves concluded from Hurpin et al., " Hurpin teaches that intradermal injection of canarypox virus does **not** work, whereas intradermal injection of naked DNA does. Thus, one skilled in the art would not expect success generally, much less success using another virus like adenovirus" (Appellant's arguments received on 4/8/02, page 16). The appellants also stated in reference to Hurpin et al. , " the canarypox data teaches away from the use of intradermal administration for viral vectors, given that intravenous administration was the only route that worked for canarypox-ps3." (Appellant's response received on 4/8/02, page 18). Thus, appellant's statements of record contradict the argument made in the appeal brief on page 9 that Hurpin et al. does not provide evidence to demonstrate the inoperability of an adenovirus vector. According to appellant's remarks of record as quoted above, the Hurpin et al. data support the unpredictability of generating anti-

tumor immune responses by intradermal injection of viruses, including adenovirus, encoding a tumor suppressor gene product.

The appellant further argues that the working examples provided by the specification demonstrate the propensity of adenovirus for dendritic cells and that post-filing evidence by Gilbert et al. demonstrates that intradermal injection of an adenovirus encoding the CS antigen from the parasite *Plasmodium berghei* can generate immune responses. In regards to appellant's *ex vivo* working examples, the Office has found that a nexus cannot be found between the working examples and the methods as claimed. As discussed in section (10) above, the working examples provided utilize an *ex vivo* approach involving the intraperitoneal, intramuscular, or intravenous administration of dendritic cells transduced *in vitro* with an adenovirus encoding p53. The appellant's working examples do not utilize the intradermal injection route recited in the instant claims or directly inject the adenovirus *in vivo*. The prior art of record clearly demonstrates that the route of administration of a viral vector has substantial effects on its ability to generate an immune response against a tumor suppressor gene such as p53. Hurpin et al., discussed in detail above, demonstrates that while intravenous injection of a vaccinia virus encoding p53 can generate an immune responses, intradermal injection of the same vaccinia virus cannot. Further, the direct administration of adenovirus and the administration of dendritic cells infected with an adenovirus *in vitro* are not equivalent and a nexus cannot be drawn between applicant's *ex vivo* results and the instant methods of treating cancer by direct intradermal injection of an adenovirus comprising expression constructs. Infection of dendritic cells *in vitro/ex vivo* occurs under artificial cell-culture conditions which allow for direct contact of the dendritic cells with optimized levels of the virus. The cells are then further manipulated *in*

vitro to generate a population of cells which are known to express the encoded gene vector prior to their introduction into the subject. In contrast, the transduction of dendritic cells *in vivo* by direct administration of the adenovirus to the subject is affected by the rate of clearance of the vector from the injection site, the tropism of the vector for the target cell, the rate of cell transduction under physiological conditions, and the presence of any pre-existing immune responses to the virus itself. The specification does not provide sufficient guidance for the targeted transduction of dendritic cells following intradermal administration of an adenovirus. The specification only states generally that dendritic cells will be infected following intradermal injection or infusion of a recombinant adenovirus. Based on these substantial differences, a nexus between the *ex vivo* working examples and the *in vivo* methods as claimed cannot be found. Thus, appellant's working examples do not provide enabling support for the methods of treating cancer as claimed.

Regarding the post-filing publication by Gilbert et al. (2002), this publication demonstrates that an adenovirus encoding the CS gene from *Plasmodium berghei* is capable of inducing strong CD8+ T cell responses after intradermal injection. However, unlike the self gene products recited in the instant methods, the antigen used by Gilbert et al. is a strong parasitic antigen. Pathogenic antigens, such as the CS gene product, are highly antigenic, non-self proteins. During development, mammals develop tolerance towards self-antigens in order to prevent inappropriate and destructive auto-antigen immune responses. As a result of the substantial differences in immunogenicity between self gene products and foreign parasitic antigens, a nexus cannot be drawn between results obtained using a foreign pathogenic antigen and the applicant's claimed invention which is drawn to immunization with a self antigen.

Furthermore, the Gilbert et al. paper teaches away from the instant invention. The Gilbert et al. paper teaches that a single injection of any of the viral vectors or DNA plasmids tested is insufficient to protect mice from parasite challenge despite the fact that significant levels of anti-CS CD8+ T cell responses were present. In fact, even two injections of adenovirus encoding CS resulted in only 13% protection, which is less than that observed in naive mice (Gilbert et al., page 1042, Table 1). Gilbert et al. teaches that adenovirus encoding CS can be used in combination with another virus or DNA plasmid encoding CS for the generation of protective immune responses. The instant methods as claimed are directed to the treatment of cancer and not simply to the generation of an immune response, the skilled artisan would not accept the data of Gilbert et al. as supportive of the enablement of the instant invention as claimed.

It is noted that the appellant also refers to has a second post-filing article by Kaiserlain et al. (1999). The Kaiserlain article is primarily directed towards intradermal immunization with plasmid DNA. The only reference to intradermal adenovirus administration is found on page 174 which states that recombinant adenovirus can be administered topically by first tape-stripping the corneal layer of the skin followed by application of the adenovirus by occlusive technique. The specification does not teach these techniques. As stated in *In re Glass*, 181 USPQ 31, (CCPA 1974), if a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while the application is still pending by later publications which add to the knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention. Instead, sufficiency must be judged as of the filing date. The fact that the specific protocol disclosed in Kaiserlian is not disclosed in the specification indicates that the

specification does not support the claims as filed, but instead reflects further critical information that is essential for the artisan to practice the invention.

The appellant also argues that the specification is enabling for the use of any and all self-antigens and that the office has not presented sufficient specific evidence to establish a *prima facie* case of non-enablement for the genus of "self-antigens" in view of the guidance provided by the specification and the working examples. Please note while applicant's claims broadly recite the intradermal administration of an adenoviral particle comprising an expression construct encoding any self gene, the applicant has elected the species of tumor suppressor genes for examination in the instant application. The claims have not been amended to reflect the elected species or any tumor suppressor gene in particular. In analyzing the claims as written, however, the office has in fact determined whether the instant specification provides an enabling disclosure for the full scope of the claims. In section (10) above, and in the preceding paragraphs of this section, the Office has set forth specific evidence as to why the guidance provided by the specification, the working examples, and the evidence provided by the appellants in the form of post-filing publications does not in fact enable the instant methods as claimed. In regards to the recitation of self gene products in the appellant's claims as they relate to the treatment of tumors, the Office has relied on the teachings of Vogelstein et al. and Restifo et al. to demonstrate that in view of the heterogeneity of tumor suppressor and oncogene mutations in a particular tumor cell and the various mechanisms by which tumor cells evade immune responses, the skilled artisan would have considered it unpredictable at the time of filing to treat any type of tumor by generating immune responses according to the instant methodology to any tumor suppressor gene or any other self-gene product. As previously noted, many tumors demonstrate impaired

antigen presentation due to loss or down-regulation of MHC, LAMP, proteosome, and antigen expression. The appealed claims recite that the cancer or pre-cancerous disease to be treated is characterized by altered or increased expression of the self-gene product. The term altered encompasses both increased or decreased expression , or no expression at all. Immune effector cells identify their targets based on the presence of appropriate forms of the target antigen on the target cell surface. Lack of expression of the target antigen would effectively hide the tumor from any tumor specific immune effector cells. Further, even if the self-gene product is overexpressed, many tumors are incapable or impaired in their ability to appropriately present antigen for immune recognition (see Restifo et al.). In addition, the prior art of record teaches the unpredictability of generating immune responses against self-gene products due to the natural development of tolerance to self-antigens in mammals. Thus, for the reasons identified above, the skilled artisan would have considered it unpredictable to treating cancer in a human subject by intradermal injection of an adenovirus encoding a tumor suppressor gene or self gene product.

In conclusion, the Office has analyzed the specification in direct accordance with the guidelines established in the MPEP and in direct accordance with the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the art for the finding of a lack of enablement for the scope of the instant methods. Thus, the Office has met its burden in providing substantial and specific evidence that the specification does not enable the scope of the claims as written. In particular, the analysis and discussion presented in the present and previous office actions specifically explains why applicant's disclosure does not reasonably

correlate with the scope of the claims as written. Based on the art recognized unpredictability in achieving targeted gene delivery *in vivo* using vectors currently available at the time of filing, the art recognized unpredictability of immunotherapy of cancer, the nature of self antigens and tumors, the breadth of the claims, the absence of guidance for the targeted transduction of dendritic cells *in vivo* using an adenovirus wherein the resulting transduced dendritic cells are capable of generating a therapeutic anti-tumor immune response, and the evidence of record that intradermal injection of recombinant viruses encoding p53 does **not** result in anti-p53 immune responses, it would have required undue experimentation for the skilled artisan at the time of filing to practice the instant methods as claimed.

For the above reasons, it is believed that the rejections should be sustained.

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